

## **Synopsis and statistical analysis plan**

**Official title:** Investigator-blinded Randomized Controlled Trial Examining the Safety and Feasibility of Different Exercise Training Programs in Patients Who Have Survived COVID-19

**Brief title:** Feasibility and Safety of High-intensity Exercise Training in Patients Surviving COVID-19

**Study identifier:** H-20033733 (amendment number: 75799)

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## **Background**

The novel coronavirus disease 2019 (COVID-19) has caused a global pandemic with millions of cases worldwide. Clinically, COVID-19 may cause pneumonia with an intense systemic inflammatory response and subsequent organ damage, including cardiac injury and remodeling. Scientifically based guidance for the rehabilitation of numerous COVID-19 survivors that are currently emerging is nonetheless sparse. Of note, it is currently unknown if the cardiopulmonary changes and morbidity in patients that initially survive COVID-19 pneumonia are reversible. Exercise training is a powerful stimulus to improve cardiorespiratory fitness, and exercise furthermore elicits a strong anti-inflammatory response, which may potentially either reduce or reverse the cardiac changes following COVID-19 pneumonia. Both low- and moderate intensity exercise is associated with protection against chronic diseases, and clinical trials have thus generally reported greater improvements after high compared to moderate intensity exercise training. Studies already showed that cardiopulmonary rehabilitation immediately following acute care admission is both safe, feasible and effective as there is seen significant improvements on physical performance and subjective health following COVID-19.

## **Aim**

The aim is to clarify the feasibility and safety of three training protocols (10-20-30; 3 x 5 min vs. 6 x 1min vs. 4 x 4min) in COVID-19 survivors. The investigators hypothesize that patients surviving COVID-19 will be able to comply to all training protocols. If feasibility and safety between training protocols are not statistically different based on the 'red-amber-green system', the investigators will choose the protocol based on the investigators experience.

## **Study design**

This study uses a randomized crossover trial testing the feasibility of 3 different training protocols. The study consists of 4 visits with 1 baseline session and 3 different training sessions performed on 10 individuals following hospital admission for COVID-10 pneumonia. Each training is separated by a 1-week washout.

## **Sample size considerations**

A sample size of 10 is based on what is feasible in the local context and will allow us to be relatively precise in our conclusions regarding feasibility outcomes. Recruitment is terminated when 10 persons have been randomly allocated or until November 15<sup>th</sup>

## **Randomization, Allocation and Blinding**

Participants are randomly allocated following successful completion of the baseline measurements. A researcher, that is not involved in testing or training procedures, generates a computer-generated block randomization schedule with balanced permutations stratified by sex (Web site Randomization.com (<http://www.randomization.com>)). To ascertain allocation concealment, the block sizes will not be disclosed. The schedule is forwarded to a research assistant, who is not involved in any study procedures and stored on a password protected computer. Following the baseline measurements, the participants are given consecutive numbers. These are forwarded to the research assistant, who returns the corresponding allocation sequence to

the study coordinator. The participants are blinded for treatment allocation until treatment assignment (following the examinations on the training days). However, following the initial two treatments blinding of the participants is no longer possible. All study personal involved with data collection will be blinded during baseline testing.

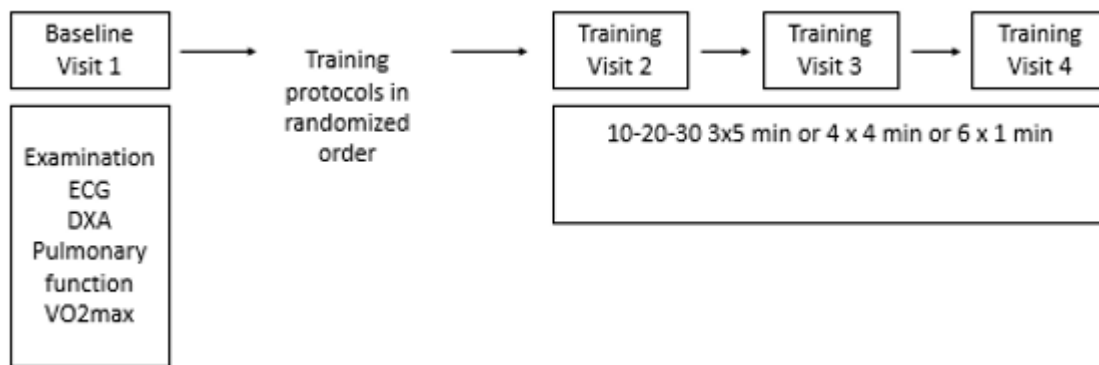


Figure 1: Study overview and tests

#### Participants:

Eligibility of study participants	
Inclusion criteria	Exclusion criteria
<p>Age <math>\geq 40</math> years</p> <p>A laboratory-confirmed initial positive test followed by one negative tests of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) <math>\leq 6</math> months after hospital discharge</p> <p><math>\leq 10</math> L oxygen requirement during hospitalization</p>	<p>Present atrial fibrillation</p> <p>Diagnosed with acute myocarditis</p> <p>Health conditions that prevent participating in the exercise intervention</p> <p>Patients who cannot undergo MR scans (e.g. kidney disease or metallic implants)</p> <p>Treatment with IL-6 receptor antagonists (tocilizumab, kevzara) within the last month due to drug interference with the cardiopulmonary exercise adaptations.</p>

Table 1: Overview of inclusion and exclusion criteria

#### VO<sub>2</sub>max protocol:

The participants will undergo a graded VO<sub>2</sub>max test on a bicycle ergometer. The test starts with a 5-minute warm-up at 30W for women and at 50W for men. Warm-up is immediately followed by a 20W increase every

1 min until exhaustion.  $\text{VO}_{2\text{max}}$  is reached when two of the following criteria are reached:  $\text{RER} > 1.10$ , plateau in oxygen consumption ( $\leq 150 \text{ ml} \cdot \text{min}^{-1}$ ) or Borg scale  $< 17$ .

### Training protocols

The 10 participants will test the feasibility of the 3 different training protocols. The exercise workload is set according to the patients  $\text{HR}_{\text{max}}$  or  $\text{watt}_{\text{max}}$  from the  $\text{VO}_{2\text{max}}$  test. All training protocols start with a 10-minute warm up and a 5-minute cool-down period. The intervals in the training protocols are interspersed with a 3-minute active rest. The accumulated time spend with a heart rate  $> 85\%$  of  $\text{HR}_{\text{max}}$  will be evaluated to determine the intensity.

	4x4 min	6x1 min	10-20-30 3x5 min
<b>Total time</b>	38 min	38 min	38 min
<b>Warm-up</b>	10 minutes warm up with a heart rate of 60-70% of $\text{HR}_{\text{max}}$	10 minutes warm up on 30% of watt-max	10 minutes warm up at 60-70% of $\text{HR}_{\text{max}}$
<b>Intervals</b>	4 intervals of 4 minutes at an intensity that will induce at least 85% of $\text{HR}_{\text{max}}$ (we will start with 75% of watt max). Each interval is separated by 3-minute active pauses, biking at 50-70% of $\text{HR}_{\text{max}}$ .	6 intervals of 1 minute at 100% of the watt-max. Each interval is interspersed by 3-minute active pauses at 30% of watt-max.	3 intervals of 5 minutes interspersed by 3 minutes on 50-70% of $\text{HR}_{\text{max}}$ . Each interval consists of 5 minutes of 5 repeated 30-20-10 intervals, consisting of 30 seconds at easy pace, 20 seconds at medium pace and 10 seconds at all-out.
<b>Cooldown</b>	3-minutes cooldown at ~ warm up intensity	7-minutes cooldown at ~ warm up intensity	7-minutes cooldown at ~ warm up intensity
<b>Success criteria</b>	The participant needs spend at least 25% of the training time above 85% of $\text{HR}_{\text{max}}$  The participant needs to reach 85% of $\text{HR}_{\text{max}}$ during the first 3 min of each 4-minute interval. If the participant does not reach 85% of $\text{HR}_{\text{max}}$ the last minute of the 4-minute interval, the watt will be upgraded based on how far	The participant needs to hold RPM above 60 in each interval. If the patient is not capable of keeping the right pace, the watt will be downgraded by 10% from the next interval.	The participant needs spend at least 25% of the training time above 85% of $\text{HR}_{\text{max}}$

	the heart rate is from the desired zone. Likewise, the watt will be downgraded if the RPM falls below 60 or in the next interval if the HR spikes above 90 % of HR <sub>max</sub>		
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Table 2: The three different high intensity interval training protocols

## Outcomes

### Feasibility and fidelity evaluation

The primary endpoint is a composite of i) participant adherence to the training dose (duration and intensity), ii) adverse events and iii) a 10-point Likert scale (see the yellow-amber-green section for details).

Key secondary outcome is the 10-point Likert scale, which evaluates enjoyment and perceived tolerance of each training protocol at the end of each training session using a 10-point Likert scale, which is one of the most fundamental and frequently used psychometric tools in social science research. Patients have to indicate the degree to which they agreed with the following statement before training: “How motivated are you for today's training?” following two statements after the training: “How enjoyable have today’s training session been?” and “How tolerant has today’s training been?”

Other outcomes to further evaluate feasibility and fidelity include success criteria for each protocol. The success criteria are defined based on prior work. Verification of training intensity is evaluated by rate of perceived exertion after each interval (6-20 Borg scale) and after completed training (1-10 Borg scale), and from accumulated minutes in the predefined heart rate zones.

Functional capacity of the patients is another outcome which is assessed with the Post COVID-19 Functional scale, which is a scale to measure the consequence of the disease beyond binary outcomes.

The primary composite outcome will be based on the ‘red-amber-green system’, that is designed to evaluate the specific training session/intervention. After a participant has completed a training session, the session will be ranked as red, amber or green based on 3 parameters: 1) Likert scale 2) Adverse events 3) Dosage reduction/adherence. Whichever category the specific training session scores the lowest in will the rating of the training.

	Red	Amber	Green
Likert scale (Tolerance)	1-2	3-4	5+
Adverse events	If the patient experiences angina, must stop the training due to any adverse event or has ST depression on the post training ECG	If $\geq 3$ adverse events are registered during the training session	If $\leq 2$ adverse events are registered during the training session

<b>Dosage reduction</b>	If $\leq 50\%$ of the total training is completed	If 50-85% of the training is completed	If $\geq 85\%$ of the training is completed
<b>Specific dosage reduction for 4x4min</b>	If HR has been over 85% of max $< 15\%$ of the time during the intervals ( $< 2:20$ )	If HR has been over 85% of max 15-24% of the time during intervals (2:20-3:50)	If HR has been over 85% of max $\geq 25\%$ of the time during intervals ( $\geq 3:50$ )
<b>Specific dosage reduction for 6x1min</b>	If the intensity must be downgraded $\geq 10\%$ in 5+ of the intervals	If the intensity must be downgraded 10% in 3-4 of the intervals	If the intensity must be downgraded 10% in $< 3$ of the intervals
<b>Specific dosage reduction for 10-20-30</b>	If HR has been over 85% of max $< 15\%$ of the time during the intervals ( $< 2:15$ )	If HR has been over 85% of max 15-24% of the time during intervals (2:15-3:40)	If HR has been over 85% of max $\geq 25\%$ of the time during intervals ( $\geq 3:40$ )

Table 3: Red-amber-green system

## Safety

Before performing any exercise the supervisor will evaluate whether the patient should participate based on an evaluation of the patient in relation to the contraindications and precautions identified below:

Training contraindications and precautions:

- Unstable angina or myocardial infarction (ECG is taking at baseline and the patient is asked for any angina-like symptoms before and after training)
- Systolic blood pressure  $> 200$  mmHg  $\pm$  diastolic blood pressure  $> 100$  mmHg (blood pressure is measured at baseline)

Training termination criteria:

- Onset of angina or angina-like symptoms.
- Signs of poor perfusion: confusion, nausea, lightheadedness, central cyanosis
- Patient requests to terminate (e.g. intolerable dyspnea)
- Physical or verbal manifestations of severe fatigue

## Measurement

**Baseline (visit 1): (in the following order)**

- Age, sex, height, weight
- Hours of sleep
- Activity level before and after hospital discharge
- Post-COVID-19 Functional Scale (PCFS)
- Standard values in rest: blood pressure, SAT, HR
- ECG
- Body composition analysis (DXA scanning: total body fat mass, lean body mass and mineral bone mass density and BMI)

- Pulmonary Function (dynamic spirometry, whole body plethysmography, diffusing capacity)
- Cardiorespiratory fitness (VO<sub>2</sub>max, watt max and HR<sub>max</sub>)

#### **Training days (visit 2, 3 and 4):**

- Saturation during training
- ECG after end training
- COVID-19 specific symptoms before and after the exercise training
  - Dyspnea, palpitations, chest pain
- Training outcome (fill out the training scheme)
  - Median watt and median HR during the training (warm-up and cool-down excluded)
  - Time spent in predefined heart rate zones
  - Post-COVID-19 Functional Status scale
  - RPE during (6-20 Borg scale) and after ended training (1-10 Borg scale)
  - Dose-reduction based on defined success criteria
  - Adverse events and termination of training (termination of training is measured in % of completed training)
  - Primary outcome: Motivation: Likert scale 1-10 before and after the workout to determine how motivated the participants are before training and how tolerant and enjoyable the training has been.

#### **Analyses**

Feasibility of the protocols will be evaluated by a composite primary endpoint including i) participant adherence to the training dose (duration and intensity), ii) adverse events and iii) a 10-point Likert scale that will be compared for the three protocols using a  $\chi^2$  test. Details of the composite primary endpoint can be found in the outcome section/the “red-amber-green” document.

The protocols will secondarily be compared using ANCOVA modeling as well as paired T testing or  $\chi^2$  test with respect to the individual endpoints e.g. Likert scale (key secondary outcome), rate of perceived exertion (RPE), Post-COVID-19 Functional scale (PFAS). The baseline value will be included as a confounder.